Adrenal Hyperplasia NOS

Introduction

This lesson will cover pheochromocytoma (the malignancy of the adrenal medulla) and the exceedingly rare MEN syndromes (seen more often on licensing exams than in any patient population), and then go into a lot of detail regarding congenital adrenal hyperplasia. Congenital adrenal hyperplasia is more common than MEN syndromes in life and has a correspondingly disproportionately high incidence on licensing exams—and for a good reason. CAH affords an overlap of endocrinopathies and metabolic pathways. It isn't that the disease itself is common or worth so much attention, but it provides such an elegant intersection of hormone regulation and phenotypic output that one case of CAH can be used to easily assess your knowledge of all the systems.

Pheochromocytoma

Pheochromocytoma ("pheo" for short) is an autonomously secreting tumor of the adrenal medulla—of **chromaffin cells**—that secretes **catecholamines**. Catecholamines, specifically epinephrine in this case, circulate throughout the bloodstream, activating adrenergic receptors everywhere. Catecholamine excess due to pheo tends to be **sporadic, paroxysmal**, and **short-lived**. Thus, the patient has no symptoms for most of the day, then has sudden surges of catecholamines released from the pheo, resulting in the activation of sympathetic receptors.

The main symptoms are due to the effects of epinephrine on the vasculature and heart. Stimulation of β_1 receptors on the heart leads to tachycardia, which increases the mean arterial pressure. Stimulation of β_1 receptors on the heart also increases contractility, further increasing mean arterial pressure. Stimulation of α_1 receptors on blood vessels induces vasoconstriction, increasing systemic vascular resistance, which further increases mean arterial pressure. Thus, it is the rise in blood pressure that predominates in the disease. Vasoconstriction can also cut off blood supply to distal extremities.

The symptoms of pheo can be recalled by the "6 P's:" p**aroxysms** (sporadic, short-lived) of p**ressure** elevations (the blood pressure is really high) that cause p**ain** (headaches from the high blood pressure), p**alpitations** (heart rate and contractility are up), p**allor** of distal extremities (vasoconstriction), and p**erspiration** (another P that the sympathetic nervous system induces, although if absent, does not alter your suspicion of the diagnosis).

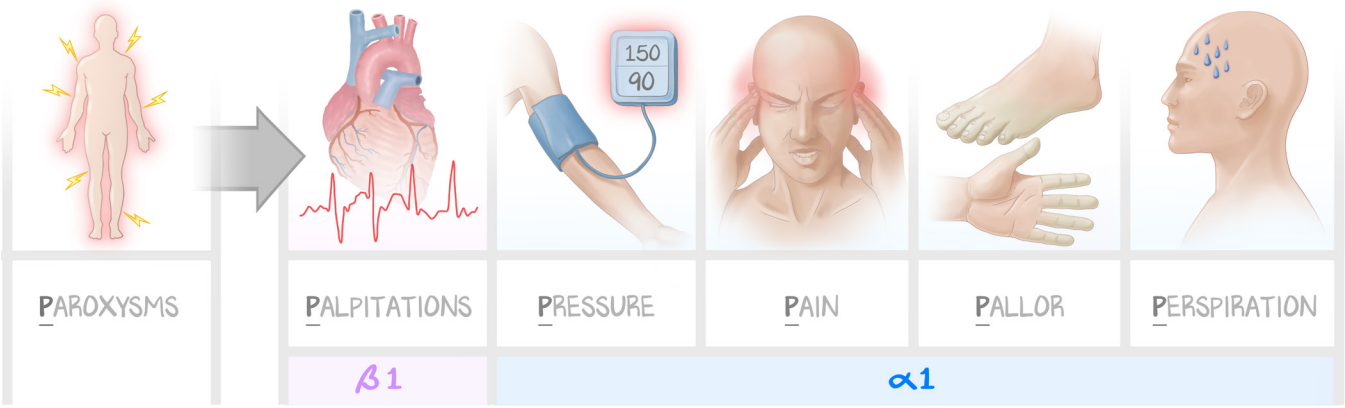

Figure 4.1: Pheochromocytoma
The symptoms are those induced by catecholamine stimulation of the vasculature and heart. Tachycardia results from β_1 stimulation. The other symptoms are driven by α_1 stimulation. Increased systemic vascular resistance cuts off blood supply to the distal extremities, causing skin changes. Increased vascular resistance causes the pressure to increase, resulting in headaches.

Norepinephrine and epinephrine are metabolized by the same enzymes **Monoamine oxidase** (MAO) and **COMT** (don't worry about the full name, recognize it only as COMT until we get to Neuroscience and study Parkinson's). In this pathway, (nor)epinephrine is converted to (nor)metanephrine, and the final product is vanillylmandelic acid (VMA). The catecholamines themselves are short-lived; these metabolites are not. Thus, the diagnosis can be made by looking for **serum metanephrines** or **24-hour urinary metanephrines and VMA**. When there is a high index of suspicion, plasma free metanephrine is chosen, and when suspicion is low, urine fractionated metanephrine and catecholamines may be a better option. If asked to choose on a licensing exam, pick the 24-hour urine (less prone to variation in catecholamine levels from other causes). The idea is, if they are symptomatic right now in front of you, get the serum levels. If they are complaining of having been symptomatic, get the 24-hour urine.

After proving elevated catecholamines, you then have to find the lesion. The imaging modality of choice is an **abdomen and pelvis CT with contrast**. If the CT is negative, reconsidering the diagnosis is the first step; however, if suspicion of a catecholamine-secreting tumor is high, the next step should be an **MIBG scan.** MIBG stands for iodine-123-metaiodobenzylguanidine. Learn MIBG scan, say MIBG scan. MIBG has a molecular structure similar to that of catecholamines (somewhere between norepinephrine and epinephrine), and so clusters in the place where a lot of catecholamines are being made. Because it uses radioactive iodine to locate the pheo, and the thyroid is the only organ that takes up iodide, in order to avoid accidental harm to the thyroid, the thyroid is saturated with iodide via the administration of potassium iodide before the administration of the radiotracer.

Treatment involves **α-blockade** with **phenoxybenzamine** and subsequent **β-blockade with any β-blocker.** This is done preprocedurally to prevent the effects of catecholamine surges that can occur when the surgeon pokes the tumor while taking it out. The severe paroxysms caused by naturally occurring sporadic small bursts of catecholamine are nothing compared to a surgeon poking the tumor with a scalpel while removing it. **Surgical resection** is required.

Pheo is associated with several gene mutations. The most classically associated gene is ***RET***, due to which pheo presents as part of the MEN2a and MEN2b syndromes (discussed below). The others are less obvious and associated with a different syndrome altogether. *VHL* is the gene mutated in von Hippel-Lindau syndrome, in which multiple renal cell carcinomas develop (you should think of *VHL* as a kidney disease gene that leads to multiple renal cell carcinomas early in life). *NF1* is the gene mutated in neurofibromatosis type 1, which we discuss in Neuroscience, presenting with café-au-lait spots and optic nerve gliomas (it should be learned as a brain disease).

A pheo outside the adrenal gland is called a **paraganglioma**. For your purposes, learn only pheo and assume that everything true of pheo is true of paraganglioma, except where the paraganglioma is found.

MEN Syndromes

This is purely an exercise in memorization. They are rare. Dr. Williams is proud of himself because the first patient he admitted on the first day of residency had yet-to-be-diagnosed MEN2A, and he haphazardly stumbled onto the diagnosis a week later. At the national conference that year, instead of being a poster presentation as intended, it was volunteered for the mystery diagnosis case on one of the main stages. It was so rare that the only time everyone in that room got to experience a real MEN2A case was in that room on that day. You will not see a patient with MEN syndrome in your career. But you will on your exam.

MEN1	MEN2A	MEN2B
Parathyroid	Parathyroid	Mucosal neuromas
Pancreatic (glucagon, VIP, insulin)	**Pheochromocytoma**	**Pheochromocytoma**
Pituitary (PRL, GH)	**Medullary carcinoma of thyroid**	**Medullary carcinoma thyroid**
MEN1 gene, chromosome 11 Menin if nuclear transcription factor	RET (tyrosine kinase)	RET (tyrosine kinase)
"Three hard P's"	Pheo, medullary thyroid . . . and . . . parathyroid	Pheo, medullary thyroid . . . and . . . neuromas

Table 4.1: MEN Syndromes

CAH #1: What Happens When You Don't Have Enough Hormone

This section explores the specific presentations of the congenital absence of certain hormones. There is a **deficiency of cortisol in all forms** of congenital adrenal hyperplasia. **Aldosterone** is found in excess in one, but deficient in another. **Androgens** are found in excess in one, but deficient in another.

In the absence of **cortisol**, the patient will present with **lethargy, hypoglycemia**, and **hypotension**. Congenital adrenal hyperplasia, because of the deficiency of cortisol, also impacts the adrenal medulla. Cortisol is required to promote the conversion of norepinephrine to epinephrine. Without cortisol, circulating epinephrine falls. Not only do the α_1 receptors work poorly without cortisol, but the circulatory hormone that activates them also isn't synthesized, further disposing the patient to hypotension.

Aldosterone Absence. In the absence of aldosterone, there is salt wasting in the collecting duct. Salt wasting leads to volume depletion. As the posterior pituitary senses volume depletion, ADH is released, which reabsorbs water from the collecting duct, thereby diluting the plasma. This is where the distinction between "*aldo, sodium, volume*" and "*ADH, water, osmolarity*" is crucial. Baby loses volume (preload), so they will have hemodynamic symptoms. The normal reflex isn't present—ADH is secreted as usual, but aldosterone is not. Baby loses volume (no aldosterone) and dilutes the blood (yes ADH). The absence of aldosterone equates with the absence of ENaC channels in the collecting duct. No sodium reabsorption also means no potassium secretion, resulting in hyperkalemia. Therefore, the **absence of aldosterone** results in **hyperkalemia** (ENaC channel), **hypovolemia** (salt wasting), and **hyponatremia** (ADH effect).

Aldosterone Excess. In abundance, aldosterone will increase salt reabsorption, resulting in excess volume expansion and leading to hypertension. The excess ENaC channel activity results in hypokalemia—more sodium reabsorbed, more potassium kicked out. Thus, in **aldosterone excess,** there are **hypokalemia and hypertension**.

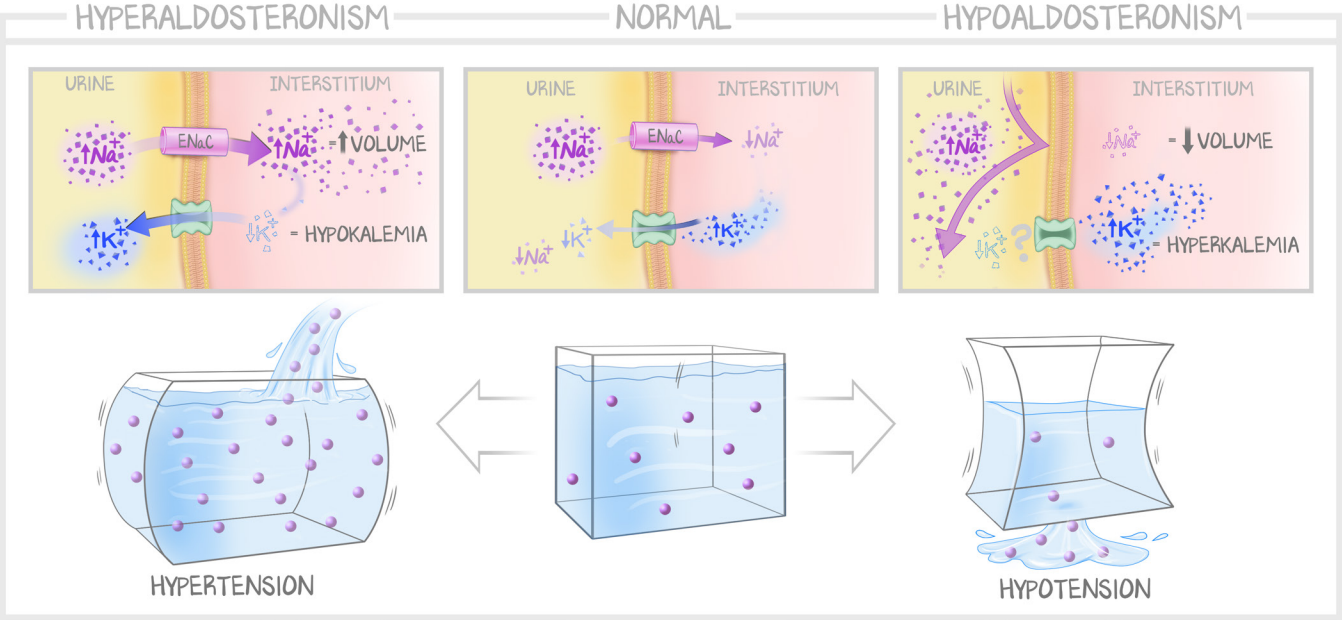

Figure 4.2: Aldosterone Excess and Deficiency
A review of the effects of hyperaldosteronism—hypertension and hypokalemia—and hypoaldosteronism—salt wasting, hypotension, and hyperkalemia. Sodium = volume. When excess sodium is reabsorbed, there is excess volume in the tank. When excess sodium is wasted in the urine, there is excess volume in the toilet and, therefore, less volume in the tank.

Androgens. XX is the genotype that will produce the XX phenotype—clitoris, vagina, labia; ovaries, fallopian tube, uterus. The XX phenotype is the default. XY is the genotype that will produce the XY phenotype—penis, scrotum; testes, vas deferens, epididymis. The XY phenotype requires the activity of genes found on the Y chromosome; in other words, XY genotypes need something extra to obtain the XY phenotype rather than the default XX phenotype. If they don't have that something extra, the phenotype will be more like that of XX. The XX genotype does not need something extra to obtain the XX phenotype. But if XX genotypes are exposed to that something extra that turns the XX phenotype to one of XY, the phenotype will be more like that of XY.

Adrenal androgens give the genitalia the XY phenotype. Gonadal androgens give the internal organs the XY phenotype. Because this is an adrenal disease, the internal organ phenotypes will match the genotype. Only the external genitalia are affected in CAH, and then, only in the right pairing of androgen excess/deficiency with genotype XX/XY.

An XX genotype will produce the XX phenotype in **androgen deficiency** and produce a more XY phenotype in **androgen excess**. This is most easily identified at birth as **ambiguous genitalia**. The process when the XX phenotype becomes more like that of XY is termed **virilization**.

An XY genotype will produce the XY phenotype in **androgen excess** and produce a more XX phenotype in **androgen deficiency**. This is most easily identified at birth as **ambiguous genitalia**. The process when the XY phenotype becomes more like that of XX is called **feminization**.

Additionally, as the child ages, androgens facilitate secondary sex characteristics. Often discovered at birth, the adrenal problem continues to affect these children. **XY** genotypes with androgen excess will undergo **precocious puberty**. XX genotypes with androgen excess will experience **hirsutism**. XX and XY genotypes with androgen deficiency will fail to develop secondary sex characteristics.

XX		XY	
Androgen Excess	Androgen Deficiency	Androgen Excess	Androgen Deficiency
Virilization	XX at birth	XY at birth	Feminization
Ambiguous genitalia	XX at birth	XY at birth	Ambiguous genitalia
XX repro organs	XX repro organs	XY repro organs	XY repro organs
Precocious puberty	Lack secondary sex	Precocious puberty	Lack secondary sex

Table 4.2: Androgen Syndromes by Sex

Adrenal glands. In all cases of CAH, the adrenals hypertrophy bilaterally, sometimes increasing to 10–15 times their normal weight due to the sustained elevation in ACTH. The adrenal cortex will be thickened and nodular—some regions undergo hyperplasia, and some don't, so the growth is irregular. On cut section, the widened cortex appears brown because of the total depletion of all lipid. There will be numerous proliferating cells, but these are either lipid-laden clear cells (the ones able to make a product) or eosinophilic lipid-less cells (the ones unable to synthesize the product).

Anterior pituitary. In addition, hyperplasia of corticotropes (ACTH-producing cells) is present in the anterior pituitary in most patients with CAH. Because of the sustained elevation in ACTH, **skin hyperpigmentation** is a possible finding. It is not seen at birth but may develop later in life. It is often a sign that insufficient supplemental cortisol is being provided and can occur at any time throughout their lifespan, but it is definitely not something seen at birth. Kids who survive this disease will be deficient in the hormones their entire life, and normal function is maintained only by exogenous supplementation.

CAH #2: A Map You Can Read

The point of this section is to simplify the biochemistry so you can focus on the outcome. In the section that follows, we will combine the logic learned in the section above with the pathways described in this section to demystify congenital adrenal hyperplasia. We're going to use "enzyme codenames" instead of their long, intimidating names. We're also going to reveal that what they do is embedded in the name of the gene that codes for them, which is where our codename comes from. This is going to feel silly, but it is necessary for the majority of students to feel like they have mastered this content.

The map starts at cholesterol. ACTH makes cholesterol into a thing. That thing's name is irrelevant. There are three paths from the first thing: down (makes aldosterone), right (makes androgens), and right and down (makes cortisol).

Only one enzyme is required to go right, coded by the *CYP17A1* gene, codenamed **Enzyme 17**. Enzyme 17 performs both the 17α-hydroxylase step and the 17,20-desmolase step. Two enzymes are required to go down. One is encoded by the *CYP21A2* gene, codenamed **Enzyme 21**. Enzyme 21 performs the 21α-hydroxylase step. Another is coded by the *CYP11B1* gene, codenamed **Enzyme 11**. Enzyme 11 performs the 11β-hydroxylase step. A deficiency in any of these three genes will result in the absence of cortisol—losing a right or a down loses cortisol. A deficiency in the genes that go right will result in the absence of cortisol and androgens, but an excess of aldosterone. A deficiency in the genes that go down will result in a deficiency of cortisol and aldosterone, but an excess in androgens.

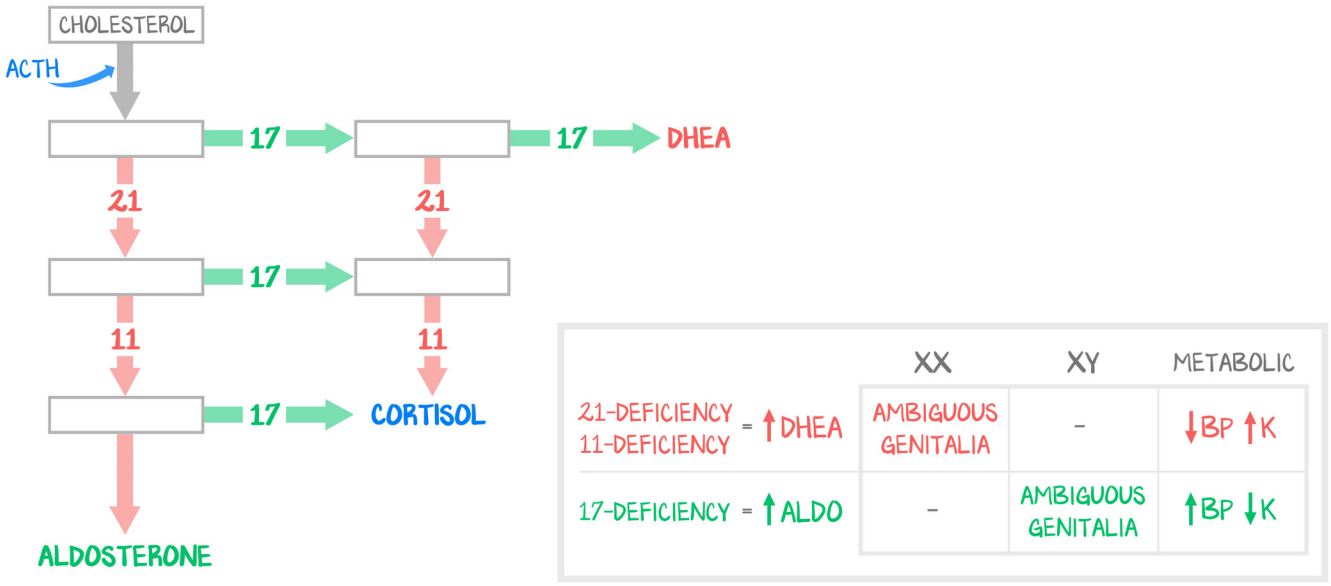

Figure 4.3: Symptoms of Congenital Adrenal Hyperplasia
Cortisol cannot be made. ACTH drives the production of cortisol precursors. Excess ACTH causes hyperpigmentation. In each CAH, either aldosterone can be made or DHEA can be made. The one that is made is made in great excess. If Enzyme 17 is broken, aldosterone excess causes hypertension and hypokalemia. Aldosterone excess necessitates DHEA deficiency, causing the XY genotype to obtain the XX phenotype. If Enzyme 21 or 11 is broken, DHEA excess causes the XX genotype to obtain the XY phenotype, although it has no outward effect on the XY genotype. DHEA excess necessitates aldosterone deficiency, resulting in salt wasting, hypotension, and hyperkalemia. These are the only three congenital adrenal hyperplasia syndromes you are to learn.

CAH #3: Congenital Adrenal Hyperplasia Syndromes

We are presenting these conditions as if there were a total loss of the enzyme. Various mutations may lead to a simple decrease in enzyme activity, which would cloud the picture. This subject is daunting as is, so we are presenting these conditions only as two genes deleted, no enzymatic activity, period.

The most common cause of CAH (90% of cases) is a defect in **Enzyme 21** (21α-hydroxylase), the enzyme needed to go **down at all**. Without Enzyme 21, neither mineralocorticoids (aldosterone) nor glucocorticoids (cortisol) can be made. No aldosterone means **hypotension, hyponatremia,** and **hyperkalemia**. No cortisol means **hypoglycemia, lethargy**, and more hypotension. But because the signal to make more cortisol (ACTH) continues, the adrenal glands make the only steroid hormone they can in excess. **Androgens** are made in excess. XY-genotype patients go unnoticed phenotypically. Before prenatal genetic screening, males had the worst prognosis because the diagnosis would go unnoticed in the newborn nursery, then severe salt wasting would cause shock before the first postnatal clinic visit. XX-genotype patients become more XY phenotypically and present with ambiguous genitalia. The internal reproductive organs are normal. Screening for **17-OH-progesterone**, the precursor molecule acted upon by 21α-hydroxylase, is the preferred screening tool for this CAH. Cholesterol, aldosterone, DHEA, cortisol, and this precursor are the only named molecules in this pathway you should remember.

A deficiency in **Enzyme 11** (11β-hydroxylase) prevents the ability to go **down all the way**. Without Enzyme 11, aldosterone and cortisol cannot be made. Did you see the switch in language? Aldosterone and cortisol cannot be made, but mineralocorticoid and glucocorticoid precursors can. The mineralocorticoid precursor does affect mineralocorticoid receptors, such that there is no salt wasting or frank hypotension. The glucocorticoid precursor does not have sufficient glucocorticoid activity,

and so the patient may present with **lethargy** and **hypoglycemia**, but usually not hypotension. This is the second most common form of CAH and often presents with premature puberty in XY-genotype patients and virilization of XX-genotype patients. Because the signal to make more cortisol (ACTH) continues, the adrenal glands make the only steroid hormone they can in excess *(the remainder of this paragraph is a repeat of the last paragraph because the result is the same)*. **Androgens** are made in excess. XY-genotype patients go unnoticed phenotypically. Before prenatal genetic screening, males had the worst prognosis because the diagnosis would go unnoticed in the newborn nursery, then severe salt wasting would cause shock before the first postnatal clinic visit. XX-genotype patients become more XY phenotypically and present with ambiguous genitalia. The internal reproductive organs are normal.

A deficiency in **Enzyme 17** (17**α**-hydroxylase) means the patient cannot go **right**. Without Enzyme 17, neither androgens nor cortisol can be made. No cortisol results **in hypotension, lethargy,** and **hypoglycemia**. No androgens mean XX-genotype patients remain phenotypically XX, whereas XY-genotype patients undergo feminization, presenting with **ambiguous genitalia**. But because the signal to make more cortisol (ACTH) continues, the adrenal glands make the only steroid hormone they can in excess—**aldosterone**. Excess aldosterone results in **hypertension and hypokalemia**.